


 Cite this: *RSC Adv.*, 2025, 15, 12739

 Received 22nd March 2025
 Accepted 9th April 2025

DOI: 10.1039/d5ra02023a

rsc.li/rsc-advances

Photo-induced decarboxylative radical cascade cyclization of unactivated alkenes: access to CF- and CF₂-substituted ring-fused imidazoles†

 Huinan Wang,^{‡,a} Shengbao Lin,^{‡,a} Hui Hong,^a Zhangjie Hu,^a Yawen Huang,^a Xiaolan Zhang,^a Sheng-Nan Lin^{*,a} and Bin-Miao Yang^{*,b}

A mild and effective visible-light-induced decarboxylative radical cascade reaction of olefin-containing imidazoles with α -fluorinated carboxylic acids as building blocks containing CF or ArCF₂ moieties, has been developed to afford a series of monofluoromethylated or aryl difluoromethylated polycyclic imidazoles in medium to excellent yields with features of simple operation, available raw materials, and wide substrate scopes. In addition, the mechanistic experiments indicated that the methodology involved a radical pathway.

Introduction

Fluorine-containing moieties, owing to the existence of the most electronegative element, could significantly alter the physicochemical properties and biological activities of parent molecules.¹ Synthetic methods for fluorinated compounds are consistently in high demand in the fields of pharmaceutical and agricultural chemistry.² Among various fluorine-containing groups, the difluoromethylene moiety (CF₂), which can serve as a bioisoster of ethereal oxygen or carbonyl groups,³ has been regarded as a valuable candidate substituent group in the process of drug discovery.⁴ Consequently, the methods for synthesizing CF₂-substituted compounds have been well developed.⁵ Notably, the attractive benzylic difluoromethylene group (ArCF₂) has been widely identified in bioactive molecules (Fig. 1a).⁶ Alongside the development of attractive methods for direct construction of the ArCF₂ moiety, such as the direct deoxygenative fluorination of aldehydes or ketones,⁷ transition-metal-catalyzed difluoroalkylation of arenes,⁸ visible-light-promoted difluoroalkylation of arenes,⁹ and direct fluorination of benzylic C–H bonds,¹⁰ a number of effective protocols for direct incorporation of external ArCF₂ groups into parent skeletons have also been established in recent years.¹¹ Nowadays, α,α -difluoroarylacetic acids have been recognized as general and effective aryl difluoromethyl radical precursors due to their beneficial features, including stability, the generation of CO₂ as

a byproduct, and easy accessibility.¹² To incorporate ArCF₂ moieties into diverse bioactive frameworks, the development of decarboxylative radical aryl difluoromethylation reactions, which often involve heat-promoted oxidation¹³ or a photo-induced process,¹⁴ has become one of the hotspots in the field of fluorine chemistry in the last decade. In addition, significant progress has been made in the construction of C–CF bonds in recent years.¹⁵ Furthermore, methods for synthesizing CF-substituted compounds *via* decarboxylative radical monofluoromethylation using α -monofluorinated carboxylic acids have also been reported.¹⁶

Nitrogen-containing heterocyclic moieties exist in numerous bioactive molecules.¹⁷ Among them, the benzimidazole-fused polycyclic scaffolds are frequently encountered.¹⁸ In particular, the tricyclic benzimidazole skeletons have attracted extensive attention in the fields of synthetic and pharmaceutical chemistry (Fig. 1b).¹⁹ Therefore, various methods for constructing polycyclic benzimidazole skeletons have been well-developed.²⁰ Among these strategies, the direct cyclization of substituted benzimidazoles with alkenes, which simultaneously

^aCollege of Chemistry and Environment Science, Shangrao Normal University, Shangrao 334001, China. E-mail: 307192@sru.edu.cn

^bThe International Joint Institute of Tianjin University, Fuzhou, Tianjin University, Tianjin 300072, China. E-mail: bmyang@tjufz.org.cn

 † Electronic supplementary information (ESI) available. See DOI: <https://doi.org/10.1039/d5ra02023a>

‡ Both authors contributed to this work equally.

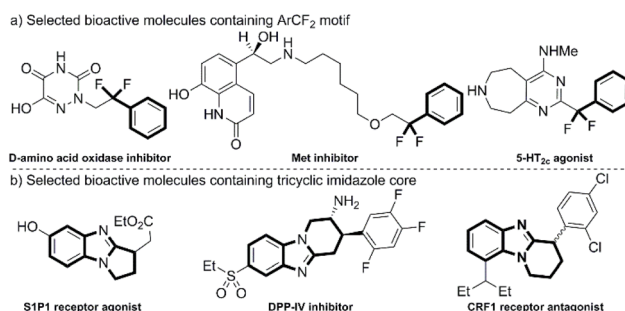


Fig. 1 Selected bioactive molecules containing ArCF₂ motif (a) or tricyclic imidazole core (b).



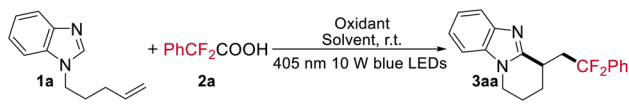
incorporates functional groups into molecules and constructs complex heterocyclic skeletons in a single-step reaction, has been considered as a convenient and atom-economical approach to access ring-fused benzimidazole derivatives with promising potential.²¹ Despite huge efforts devoted to synthesizing functionalized polycyclic benzimidazoles through radical tandem reactions of *N*-alkenoxyl 2-aryl benzimidazoles,²² studies on the intramolecular cyclization of substituted imidazoles with olefins at the C-2 position to afford ring-fused imidazoles have continued to attract more and more interest in recent years, including transition-metal-catalyzed cross-coupling,²³ and cascade radical cyclization.²⁴ In 2021, Li and co-workers described a direct radical cyclization of imidazoles with olefins to afford difluoroalkylated polycyclic imidazoles using BrCF_2COR as a radical source (Scheme 1a).²⁵ Subsequently, Chen,²⁶ Li,²⁷ and Jin²⁸ independently disclosed a series of interesting works on radical cascade cyclization of imidazoles with olefins to synthesize CF_3/HCF_2 -substituted tricyclic benzimidazoles using $\text{CF}_3/\text{HCF}_2\text{SO}_2\text{Na}$ (Scheme 1b-d). Compared to the preparation of CF_3 -substituted polycyclic imidazoles,^{26–29} the introduction of ArCF_2 groups into ring-fused imidazoles remains largely unexplored. Given the biological activities of benzimidazole core and aryldifluoromethyl group, it makes sense to incorporate ArCF_2 motif into polycyclic benzimidazole skeletons. In 2025, Li's group reported a protocol for introducing ArCF_2 groups to synthesize aryldifluoromethylated polycyclic imidazoles (Scheme 1e).³⁰ Nevertheless, Li's work exhibited several limitations, including limited substrates, unexplored scope of aryldifluoroacetic acids, low yields, excessive amounts of fluorine sources, and ambiguities in the proposed photochemical mechanistic pathway. During the

same period, motivated by ongoing interest in photo-induced synthesis of fluorinated heterocyclic compounds,³¹ we attempted to develop the protocol to synthesize CF/ArCF_2 -substituted polycyclic imidazoles through visible-light-promoted decarboxylative radical cascade cyclization of olefin-containing imidazoles with corresponding α -fluorinated carboxylic acids, simultaneously constructing $\text{C}(\text{sp}^3)\text{-CF}$ or $\text{C}(\text{sp}^3)\text{-CF}_2\text{Ar}$ bonds (Scheme 1f).

Results and discussion

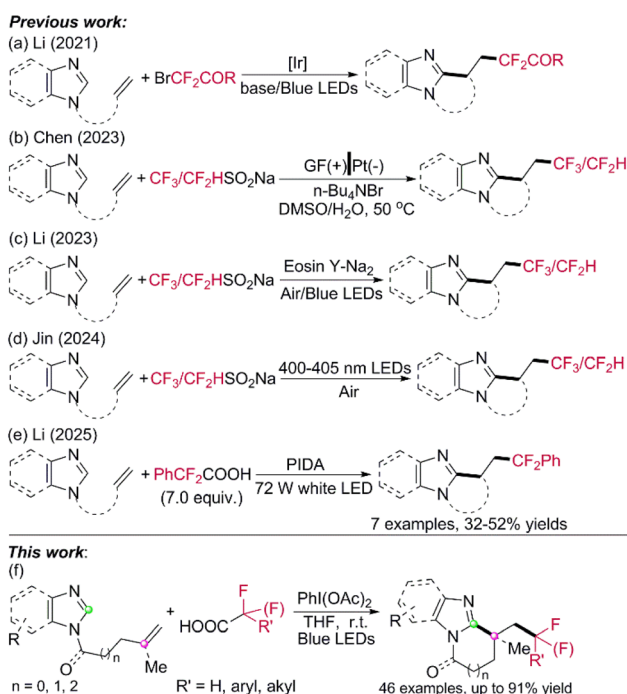
To evaluate the reaction conditions, 1-(pent-4-en-1-yl)-1*H*-benzo[*d*]imidazole (**1a**) and 2,2-difluoro-2-phenylacetic acid (**2a**) were chosen as model substrates (Table 1, details in the ESI†). Initially, $\text{PhI}(\text{OAc})_2$ was employed as an oxidant, and the reaction was conducted in THF with the irradiation of 405 nm LEDs (10w) at ambient temperature under a nitrogen atmosphere, generating the expected product **3aa** in 56% isolated yield (Table 1, entry 1). Then, other oxidants were investigated, such as $\text{PhI}(\text{OCOCF}_3)_2$ and $(\text{NH}_4)_2\text{S}_2\text{O}_8$, but no reaction was observed (Table 1, entries 2 and 3). Subsequently, we screened several common solvents, including DMSO, MeCN, DCM, and so on, but unsatisfactory results were demonstrated (Table 1, entries 4–9). Interestingly, a mixed solvent system of THF and H_2O proved equally suitable for the template reaction (Table 1, entry 10). Employing KHCO_3 as a base failed to enhance the reaction efficiency (Table 1, entry 11). Fortunately, when we decreased

Table 1 Optimization of reaction conditions^a



Entry	Oxidant	Solvent	Yield ^b (%)
1	$\text{PhI}(\text{OAc})_2$	THF	5.3
2	PIFA	THF	n.r.
3	$(\text{NH}_4)_2\text{S}_2\text{O}_8$	THF	n.r.
4	$\text{PhI}(\text{OAc})_2$	DMSO	Trace
5	$\text{PhI}(\text{OAc})_2$	DMAC	11
6	$\text{PhI}(\text{OAc})_2$	CH_3CN	n.r.
7	$\text{PhI}(\text{OAc})_2$	Et_2O	9
8	$\text{PhI}(\text{OAc})_2$	DCM	n.r.
9	$\text{PhI}(\text{OAc})_2$	Toluene	20
10 ^c	$\text{PhI}(\text{OAc})_2$	THF- H_2O	48
11 ^d	$\text{PhI}(\text{OAc})_2$	THF	54
12 ^e	$\text{PhI}(\text{OAc})_2$	THF	80(89)
13 ^f	$\text{PhI}(\text{OAc})_2$	THF	78
14 ^g	$\text{PhI}(\text{OAc})_2$	THF	79
15 ^h	$\text{PhI}(\text{OAc})_2$	THF	n.r.
16	—	THF	n.r.

^a Reaction conditions: **1a** (0.2 mmol), **2a** (0.6 mmol) and oxidant (0.6 mmol) in solvent (2 mL) irradiated with 405 nm 10 W blue LEDs at room temperature for 12 h under a N_2 atmosphere n.r. no reaction. ^b Isolated yields. ^c In THF- H_2O (2 mL, v/v, 9 : 1). ^d KHCO_3 (0.6 mmol) as additive. ^e **2a** (0.4 mmol), ¹⁹F NMR yield are given in parentheses with (trifluoromethoxy)benzene as the internal standard. ^f **2a** (0.4 mmol) 16 h. ^g **2a** (0.4 mmol) and FeCl_2 (0.02 mmol) as additive. ^h No irradiation.



Scheme 1 Synthesis of fluorinated polycyclic imidazoles from imidazoles and olefins.



the concentration of **1a**, the isolated yield of **3aa** increased to 80% (Table 1, entry 12), and a 12 hours irradiation period was adequate to achieve complete conversion of the substrate (Table 1, entry 13). However, the addition of FeCl₂ did not further improve the efficiency of reaction (Table 1, entry 14). Additionally, the reaction failed to ignite in the absence of either PhI(OAc)₂ or light irradiation, highlighting the indispensable roles of both PhI(OAc)₂ and light irradiation (Table 1, entries 15 and 16). Therefore, the optimized reaction conditions were determined as follows: the reaction mixture of **1a** (0.2 mmol), **2a** (0.4 mmol), and PhI(OAc)₂ (0.6 mmol) in THF (2 mL) was exposed to 405 nm blue LEDs (10 W) at room temperature for 12 h.

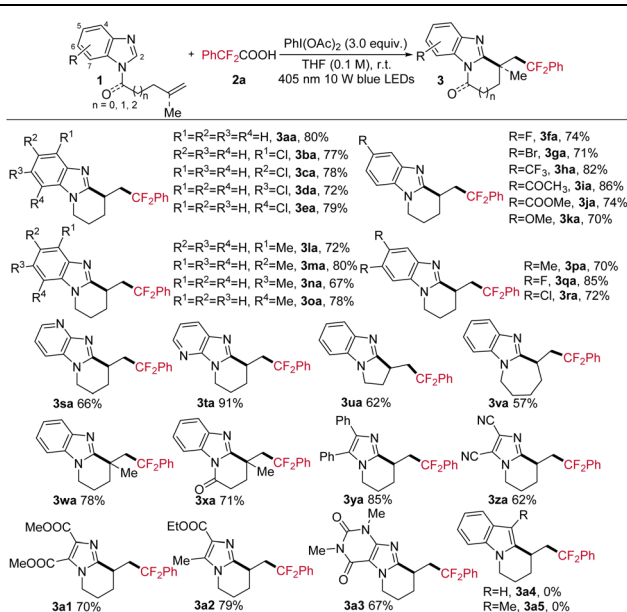
Having established the optimal reaction conditions, we then explored the scope of this oxidative decarboxylative aryldifluoromethylation/cyclization reaction with respect to substituted *N*-alkenyl benzimidazoles. As shown in Table 2, a variety of substituted *N*-alkenyl benzimidazoles with electron-withdrawing groups (F, Cl, Br, CF₃, COCH₃ and COOMe) or electron-donating groups (OMe and Me) at different positions of phenyl ring successfully underwent the decarboxylative cascade cyclization reaction, yielding the corresponding products **3aa–oa** in 67–86% yields. Pleasingly, the substrates with halogen atoms (F, Cl and Br) at different positions of aryl group proved to be well-tolerated under the standard conditions, smoothly affording the desired products in moderate yields (**3ba–ga**, 71–79%), which enable following modifications. It is worth mentioning that the substrate with electron-withdrawing groups (COCH₃) exhibited higher reactivity than the model

substrate under the optimized conditions, generating the target product **3ia** in up to 86% yield. The sterically hindered substrate with a methyl group at the 4- position of benzene ring underwent the cascade cyclization reaction smoothly, affording the corresponding product **3la** with a yield of 72%, indicating that steric hindrance has a negligible effect on this transformation. Subsequently, the 5,6-disubstituted substrates with dimethyl or dihalogen demonstrated good compatibility, and were transformed into the expected products in moderate yields (**3pa–ra**, 70–85%).

When it comes to the substrates containing 4- or 7-azo-benzimidazole core (**1s** and **1t**), the desired products (**3sa** and **3ta**) were generated in 66% and 91% yields, respectively. We then turned our attention to the modification of olefin motif. To our delight, *N*-but-3-en-1-yl benzimidazole **1u** successfully performed the tandem reaction, forming the five-membered fused product **3ua** in a considerable yield of 62%. Moreover, we successfully constructed seven-membered cyclized benzimidazole **3va** with an acceptable yield of 57%. Considering the effect of radical stability, we installed methyl group into olefin motif. However, the relative product **3wa** was obtained with a slightly decreased yield of 78%. Furthermore, when *N*-alkenoxyl substrate **1x** was employed, the corresponding product **3xa** was obtained in reasonable yield of 71%. Then, we focused on imidazole-derived substrates, and found that the desired bicyclic aryldifluoromethylated imidazoles could be obtained in moderate to good yields (**3ya**, 85%; **3za** 62%; **3a1**, 70%; **3a2**, 79%; **3a3**, 67%). These results suggested that substrates with electron-donating groups on imidazole ring were generally more reactive than those with electron-withdrawing groups (**3ya**, **3a2** vs. **3za**, **3a1**). Finally, to our disappointment, the anticipated product **3a4** could not be obtained, indicating that the *N*-alkenyl indole **1a4** was unsuitable for this transformation. To our disappointment, the anticipated product **3a4** could not be obtained, indicating that the *N*-alkenyl indole **1a4** was unsuitable for this transformation. Finally, when 3-methyl substituted *N*-alkenyl indole **1a5** was employed for this transformation, the reaction could not proceed smoothly under the present conditions, leading to obvious raw material remaining, and indicating that the indole core was probably incompatible with this protocol.

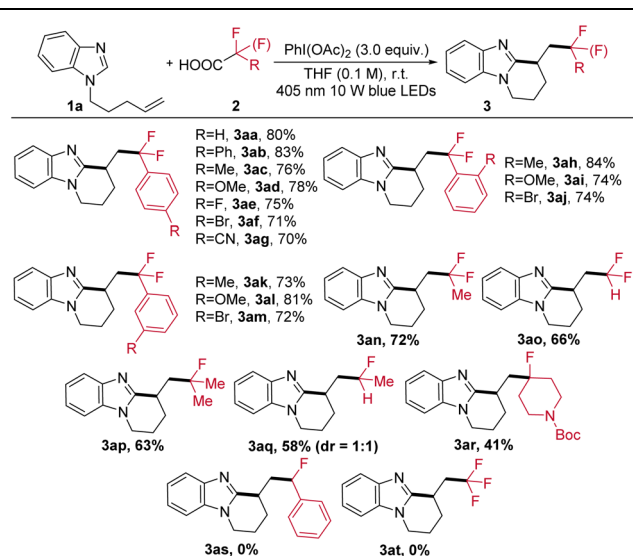
Afterwards, we investigated the scope of this reaction with respect to substituted aryldifluoroacetic acids. As revealed in Table 3, a broad range of aryldifluoroacetic acids **2b–m**, containing electron-donating (Ph, Me, OMe) or electron-withdrawing groups (F, Br, CN) at different positions of the phenyl ring, were well tolerated under the standard conditions, affording the corresponding products **3ab–am** in yields of 71–84%. Comparing substituents at the same positions of the aromatic ring, we found that the reactivities of substrates with electron-donating groups (Ph, Me, OMe) were higher than those with electron-withdrawing groups (F, Br, CN) in reaction (**3ab**, **3ac**, **3ad** vs. **3ae**, **3af**, **3ag**; **3ah**, **3ai** vs. **3aj**; **3ak**, **3al** vs. **3am**). Moreover, this protocol exhibited good tolerance to halogens (F and Br), and the corresponding products were obtained in moderate yields, offering potential for further modifications (**3ae**, 75%; **3af**, 71%; **3aj**, 74%; **3am**, 72%). To our delight, when

Table 2 Substrate scope of alkenyl imidazoles^{ab}



^a Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), and PhI(OAc)₂ (0.6 mmol) in THF (2 mL) irradiated with 405 nm 10 W blue LEDs at room temperature for 12 h under a N₂ atmosphere. ^b Isolated yields.

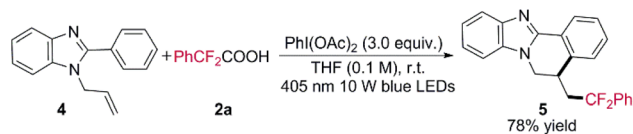


Table 3 Substrate scope of α -fluorinated carboxylic acids^{ab}

^a Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), and $\text{PhI}(\text{OAc})_2$ (0.6 mmol) in THF (2 mL) irradiated with 405 nm 10 W blue LEDs at room temperature for 12 h under a N_2 atmosphere. ^b Isolated yields.

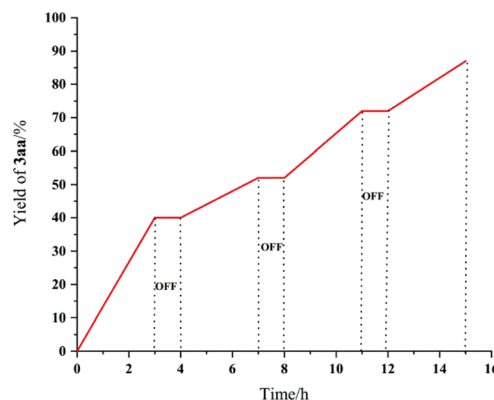
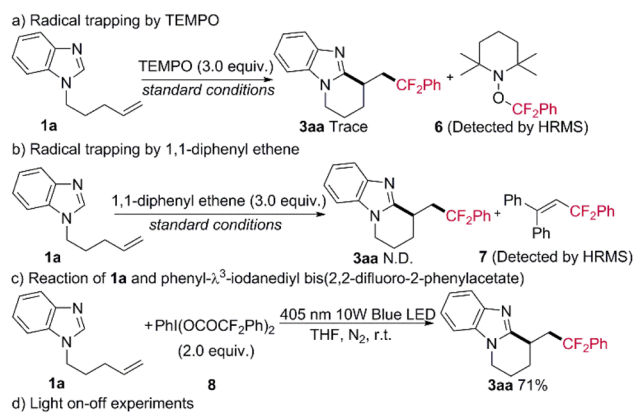
α,α -difluoropropanoic acid (MeCF_2COOH , **2n**) was used as a representative example of aliphatic difluoroacetic acids, the preparation of product **3an** proceeded smoothly under the standard conditions with a satisfactory yield of 72%. Remarkably, the difluoroacetic acid (HCF_2COOH , **2o**) also exhibited good compatibility with this cascade cyclization reaction, generating the product **3ao** in 66% yield. To further extend the application of this photo-induced decarboxylative cascade cyclization reaction to α -fluorinated carboxylic acids, we found that aliphatic α -monofluoroacetic acids, such as $\text{Me}_2\text{CFCO}_2\text{H}$ (**2p**), $\text{MeCHF}_2\text{CO}_2\text{H}$ (**2q**), and 1-(tert-butoxycarbonyl)-4-fluoropiperidine-4-carboxylic acid (**2r**), were effectively transformed into the corresponding products **3ap**, **3aq**, and **3ar**, which were obtained in 63%, 58%, and 41% yields, respectively. Regrettably, when we investigated $\text{PhCHF}_2\text{COOH}$ (**2s**), the desired reaction did not proceed with unreacted starting materials, indicating that α -fluorobenzeneacetic acid was incompatible with this protocol, possibly because the corresponding stable radical intermediate could not be continuously generated under the standard experimental conditions. Moreover, when we investigated CF_3COOH (**2t**), which has high oxidation potential, the reaction could not proceed smoothly under the standard conditions, likely due to difficulty in forming the stable radical intermediate.

To broaden the application of this strategy, we explored the construction of PhCF_2 -substituted benzimidazole-dihydroisoquinoline skeleton *via* a photo-induced decarboxylative radical cascade reaction. Encouragingly, the ring-fused tetracyclic product (**5**) was successfully prepared from *N*-alkenyl 2-phenyl benzimidazole (**4**) under the optimized conditions with a synthetically useful yield of 78% (Scheme 2).

Scheme 2 Construction of the PhCF_2 -substituted benzimidazole-dihydroisoquinoline.

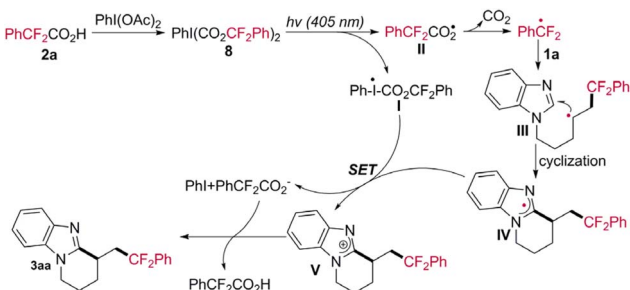
Additionally, to explore the potential synthetic utility of this protocol, a gram-scale experiment was carried out, demonstrating an isolated yield of 77% (1.44 g, details in the ESI[†]), and confirming the appropriate suitability for large-scale preparation of PhCF_2 -substituted ring-fused imidazoles.

To investigate the mechanism of this protocol, several control experiments were conducted under the standard conditions. Initially, the template reaction was remarkably suppressed by the addition of 2,2,6,6-tetramethyl-piperidin-1-oxyl (TEMPO, 3.0 equiv.) as a radical scavenger. Only a trace amount of **3aa** was detected, and radical-trapping adduct TEMPO- CF_2Ar (**6**) was identified by high-resolution mass spectrometry (HRMS) (Scheme 3a), indicating significant inhibition of the transformation into **3aa**. Moreover, the conversion from **1a** to **3aa** was completely inhibited upon the addition of 1,1-diphenylethylene as a radical scavenger (3.0 equiv.), resulting in the absence of **3aa** and the detection of compound **7** by HRMS (Scheme 3b). The results of radical-trapping experiments



Scheme 3 Control experiments.





Scheme 4 Possible reaction mechanism.

showed that the cascade cyclization reaction might be relative to a free radical process. Furthermore, the reaction of **1a** with phenyl- λ^3 -iodanediyl bis(2,2-difluoro-2-phenylacetate) (**8**) proceeded smoothly to deliver **3aa** in an isolated yield of 71% under the standard conditions, indicating that $\text{PhI}(\text{OCOCF}_2\text{Ph})_2$ (**8**) is probably the key intermediate in this conversion process (Scheme 3c). To display the role of visible-light irradiation in this transformation, an On/Off light-illumination experiment was performed. The results showed that continuous illumination is essential for the reaction to proceed (Scheme 3d).

Based on the above mechanistic studies as well as previous related literature,¹⁴ a plausible reaction pathway is proposed in Scheme 4 (taking the reaction of **1a** with **2a** as an example). Initially, the intermediate $\text{PhI}(\text{OCOCF}_2\text{Ph})_2$ (**8**) is formed by ligand exchange between $\text{PhI}(\text{OAc})_2$ and PhCF_2COOH (**2a**), simultaneously generating an oxygen-centred radical intermediate **II** and an idoine-centred radical intermediate **I** through homolysis of the C–I bond under the irradiation of 405 nm visible light. The radical intermediate **II** undergoes a decarboxylative process to generate a PhCF_2 radical, which then attacks the terminal alkenyl moiety of substrate **1a** to afford carbon-centred radical intermediate **III**. Subsequently, intramolecular radical cyclization of intermediate **III** occurs to form intermediate **IV**, which is oxidized by intermediate **I** through a single-electron transfer (SET) process, leading to the cationic intermediate **V**. Finally, deprotonation and rearomatization of intermediate **V** take place, yielding the target product **3aa**.

Conclusions

In summary, we developed an efficient and simple protocol for photo-induced decarboxylative radical coupling of unactivated olefin-containing imidazoles with α -fluorinated carboxylic acids, affording CF- or ArCF_2 -substituted ring-fused imidazoles in moderate to good yields. It was noteworthy that this practical methodology has several beneficial merits, including simple operation, readily available starting materials, and good functional group compatibility. Moreover, mechanistic experiments confirmed that this photo-induced decarboxylative radical cascade reaction proceeds *via* a radical pathway.

Data availability

The data supporting this article have been included as part of the ESI.†

Author contributions

H. Wang and S. Lin performed the experiments, compound characterization and data analysis. H. Hong, Z. Hu, Y. Huang and X. Zhang synthesized the raw materials. S.-N. Lin and B.-M. Yang finalized the manuscript.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

The authors are grateful for the financial support from the National Natural Science Foundation of China (22201205).

References

- For selected reviews: (a) P. Jeschke, *Pest Manag. Sci.*, 2024, **80**, 3065–3087; (b) G. Chandra, D. V. Singh, G. K. Mahato and S. Patel, *Chem. Pap.*, 2023, **77**, 4085–4106; (c) C. Zhang, *ACS Omega*, 2022, **7**, 18206–18212; (d) O. Kamble, R. Dandela and S. Shinde, *Curr. Org. Chem.*, 2021, **25**, 2650–2665.
- For selected reviews: (a) X. Yin, X. Wang, L. Song, J. Zhang and X. Wang, *Molecules*, 2024, **29**, 3677; (b) D. Lin, M. Coe, V. Krishnamurti, X. Ispizua-Rodriguez and G. K. Surya Prakash, *Chem. Rec.*, 2023, **23**, e202300104; (c) Purushotam, A. Bera and D. Banerjee, *Org. Biomol. Chem.*, 2023, **21**, 9298–9315; (d) P. L. Kalar, S. Agrawal, S. Kushwaha, S. Gayen and K. Das, *Curr. Org. Chem.*, 2023, **27**, 190–205; (e) T. T. Bui and H.-K. Kim, *Chem.-Asian J.*, 2021, **16**, 2155–2167.
- M. Chen, Y. Cui, X. Chen, R. Shang and X. Zhang, *Nat. Commun.*, 2024, **15**, 419–428.
- For selected reviews: (a) C. Lu, Y. Song, L. Gao and Y. Wang, *Org. Biomol. Chem.*, 2024, **22**, 8700–8713; (b) S. Ali and J. Zhou, *Eur. J. Med. Chem.*, 2023, **256**, 115476–115488; (c) C. Rao, T. Zhang and H. Huang, *Nat. Commun.*, 2024, **15**, 7924.
- For selected review: (a) L.-J. Tang, Y. Wen, H.-X. Jin, W. Luo, L. Long, J. Shen, H. Luo and D. Yu, *Org. Chem. Front.*, 2025, **12**, 2052–2075; (b) L. Shi, D. An and G.-J. Mei, *Org. Chem. Front.*, 2022, **9**, 4192–4208; (c) J. Feng, X. Jia, S. Zhang, K. Lu and D. Cahard, *Org. Chem. Front.*, 2022, **9**, 3598–3623; (d) D.-Q. Dong, H. Yang, J.-L. Shi, W.-J. Si, Z.-L. Wang and X.-M. Xu, *Org. Chem. Front.*, 2020, **7**, 2538–2575; (e) E. Oftadeh, M. J. Wong, J. Yu, X. Li, Y. Cao, F. Gallou, L. Heinz and B. H. Lipshutz, *J. Org. Chem.*, 2024, **89**, 17331–17337; (f) E. Miller, S. Kim, K. Gibson, J. S. Derrick and F. D. Toste, *J. Am. Chem. Soc.*, 2020, **142**, 8946–8952; (g) C. Xu, Z.-F. Yang, L. An and X. Zhang, *ACS Catal.*, 2019, **9**, 8224–8229.
- (a) M. Nambo, J. C.-H. Yim, L. B. O. Freitas, Y. Tahara, Z. T. Ariki, Y. Maekawa, D. Yokogawa and C. M. Crudden, *Nat. Commun.*, 2019, **10**, 4528; (b) N. Hin, B. Duvall, D. Ferraris, J. Alt, A. G. Thomas, R. Rais, C. Rojas, Y. Wu, K. M. Wozniak, B. S. Slusher and T. Tsukamoto, *J. Med.*



- Chem.*, 2015, **58**, 7258–7272; (c) P. Montuschi and G. Ciabattini, *J. Med. Chem.*, 2015, **58**, 4131–4164.
- 7 (a) P. Bhattarai, S. Koley, K. Goel and R. A. Altman, *Chem. Commun.*, 2025, **61**, 2524; (b) E. Mao, C. N. Prieto Kullmer, H. A. Sakai and D. W. C. MacMillan, *J. Am. Chem. Soc.*, 2024, **146**, 5067–5073; (c) Y. Li, K. A. Wheeler and R. Dembinski, *Org. Biomol. Chem.*, 2012, **10**, 2395–2408; (d) A. Khalaf, D. Grée, H. Abdaliah, N. Jaber, A. Hachem and R. Grée, *Tetrahedron Lett.*, 2010, **51**, 2413–2415.
- 8 For selected review: (a) Z. Feng, Y.-L. Xiao and X. Zhang, *Acc. Chem. Res.*, 2018, **51**, 2264–2278; (b) Y.-C. Luo, F.-F. Tong, Y. Zhang, C.-Y. He and X. Zhang, *J. Am. Chem. Soc.*, 2021, **143**, 13971–13979; (c) Y.-L. Xiao, Q.-Q. Min, C. Xu, R.-W. Wang and X. Zhang, *Angew. Chem., Int. Ed.*, 2016, **55**, 5837–5841; (d) Q.-Q. Min, Z. Yin, Z. Feng, W.-H. Guo and X. Zhang, *J. Am. Chem. Soc.*, 2014, **136**, 1230–1233.
- 9 (a) X.-L. Zhu, H. Wang, C.-K. Zhai and W. He, *Org. Biomol. Chem.*, 2024, **22**, 720–724; (b) Y. Cheng, X. Zhang, G. An, G. Li and Z. Yang, *Chin. Chem. Lett.*, 2023, **34**, 107625.
- 10 (a) F. Rasheed, J. Shi, T. Zeng, Y. Krishna, D. Fishlock and A. Orellana, *Org. Lett.*, 2023, **25**, 8628–8633; (b) J.-B. Xia, C. Zhu and C. Chen, *J. Am. Chem. Soc.*, 2013, **135**, 17494–17500.
- 11 (a) J. Huang, L. Fu, Z. Tang, X. Ma, X. Zhao and D. Zhao, *Chin. Chem. Lett.*, 2024, 110505; (b) J. Wang, Q. Zhou, L. Zhou and Z. Zhang, *ACS Catal.*, 2024, **14**, 18499–18506; (c) C. Guo, X. Han, X. Li, Z. Diao, X. Li and Y. Dong, *Asian J. Org. Chem.*, 2022, **11**, e202100663.
- 12 For selected reviews: (a) Y. Zhu, T. Xiao, D. Xia and W. Yang, *Chin. J. Org. Chem.*, 2022, **42**, 4067–4077; (b) W. Mei, Y. Kong and G. Yan, *Org. Chem. Front.*, 2021, **8**, 5516–5530.
- 13 (a) Q. Sun, H. Li, X. Chen, J. Hao, H. Deng and H. Jiang, *Molecules*, 2023, **28**, 3578–3591; (b) J.-W. Yuan, M.-Y. Zhang, Y. Liu, W.-Y. Hu, L.-R. Yang, Y.-M. Xiao, X.-Q. Diao, S.-R. Zhang and J. Mao, *Org. Biomol. Chem.*, 2022, **20**, 9722–9733; (c) F. Zhao, S. Guo, Y. Zhang, T. Sun, B. Yang, Y. Ye and K. Sun, *Org. Chem. Front.*, 2021, **8**, 6895–6900; (d) Z. Chen, X. Bai, J. Sun and Y. Xu, *J. Org. Chem.*, 2020, **85**, 7674–7682.
- 14 (a) Z. Song, L. Guo, C. Yang and W. Xia, *Org. Chem. Front.*, 2024, **11**, 4436–4441; (b) A. Gutiérrez-Bonet and W. Liu, *Org. Lett.*, 2023, **25**, 483–487; (c) J. Yuan, L. Shen, N. Guo, Y. Yin, P. Yang, L. Yang, Y. Xiao and S. Zhang, *J. Org. Chem.*, 2023, **88**, 16598–16608; (d) C. Guo, X. Han, Y. Feng, Z. Liu, Y. Li, H. Liu, L. Zhang, Y. Dong and X. Li, *J. Org. Chem.*, 2022, **87**, 9232–9241; (e) Q.-W. Gui, F. Teng, H. Yang, C. Xun, W.-J. Huang, Z.-Q. Lu, M.-X. Zhu, W.-T. Ouyang and W.-M. He, *Chem. - Asian J.*, 2022, **17**, e202101139.
- 15 For selected reviews: (a) B.-J. Li, Y.-L. Ruan, L. Zhu, J. Zhou and J.-S. Yu, *Chem. Commun.*, 2024, **60**, 12302–12314; (b) M. Y. Moskalik, *Int. J. Mol. Sci.*, 2023, **24**, 17593; (c) T. W. Butcher, W. M. Amberg and J. F. Hartwig, *Angew. Chem., Int. Ed.*, 2022, **61**, e202112251; (d) C. Sun, Q. Zhou, C.-Y. Li, Z.-W. Hou and L. Wang, *Org. Lett.*, 2024, **26**, 883–888; (e) T. Zeng, C. Huang, Y. Zhang, Y. Luo and D. Niu, *Green Chem.*, 2024, **26**, 8701–8705; (f) R. Wang, J. Xu, J.-X. Li, B.-B. Wu, R.-X. Jin, Y.-X. Bi and X.-S. Wang, *Chin. Chem. Lett.*, 2023, **34**, 108490; (g) J.-D. Hamel and J.-F. Paquin, *Chem. Commun.*, 2018, **54**, 10224–10239.
- 16 (a) F. Pasca, Y. Gelato, M. Andresini, D. Serbetci, P. Natho, G. Romanazzi, L. Degennaro, M. Colella and R. Luisi, *JACS Au*, 2025, **5**, 684–692; (b) H. Wang, C.-F. Liu, Z. Song, M. Yuan, Y. A. Ho, O. Gutierrez and M. J. Koh, *ACS Catal.*, 2020, **10**, 4451–4459.
- 17 For selected reviews: (a) G. Wu, W. Wang, F. Li, C. Xu, Y. Zhou, Z. Li, B. Liu, L. Shao, D. Chen, S. Bai and Z. Wang, *Molecules*, 2024, **29**, 5155; (b) S. Majee, Shilpa, M. Sarav, B. K. Banik and D. Ray, *Pharmaceuticals*, 2023, **16**, 873.
- 18 For selected reviews: (a) S. Venugopal, B. Kaur, A. Verma, P. Wadhwa, M. Magan, S. Hudda and V. Kakoty, *Chem. Biol. Drug Des.*, 2023, **102**, 357–376; (b) N. Kerru, L. Gummidi, S. Maddila, K. K. Gangu and S. B. Jonnalagadda, *Molecules*, 2020, **25**, 1909.
- 19 (a) T. Kojima, M. Mochizuki, T. Takai, Y. Hoashi, S. Morimoto, M. Seto, M. Nakamura, K. Kobayashi, Y. Sako, M. Tanaka, N. Kanzaki, Y. Kosugi, T. Yano and K. Aso, *Bioorg. Med. Chem.*, 2018, **26**, 2229–2250; (b) I. Beltran-Hortelano, V. Alcolea, M. Font and S. Pérez-Silanes, *Eur. J. Med. Chem.*, 2020, **206**, 112692–112704; (c) S. D. Edmondson, A. Mastracchio, J. M. Cox, G. J. Eiermann, H. He, K. A. Lyons, R. A. Patel, S. B. Patel, A. Petrov, G. Scapin, J. K. Wu, S. Xu, B. Zhu, N. A. Thornberry, R. S. Roy and A. E. Weber, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 4097–4101.
- 20 For selected reviews: (a) A. E. Alami, H. Sdassi and S. Bouzikri, *Synth. Commun.*, 2024, **54**, 613–635; (b) N. T. Chung, V. C. Dung and D. X. Duc, *RSC Adv.*, 2023, **13**, 32734–32771; (c) D. J. Twardy, K. A. Wheeler, B. Török and R. Dembinski, *Molecules*, 2022, **27**, 2062–2078; (d) M. Sweeney, D. Conboy, S. I. Mirallai and F. Aldabbagh, *Molecules*, 2021, **26**, 2684–2712.
- 21 For selected reviews: (a) P. V. Kumar, K. Aravindraj, G. Madhumitha and S. M. Roopan, *Curr. Org. Chem.*, 2023, **27**, 997–1009; (b) H. Liu, L. Wang and J.-T. Yu, *Asian J. Org. Chem.*, 2023, **12**, e202300101.
- 22 (a) Y. Xu, C.-J. Wang, C. Lv, J. Wang, Q. Zhang, J. Wang, R.-P. Shen, B. Sun and C. Jin, *New J. Chem.*, 2024, **48**, 14684–14689; (b) K. Sui, Y. Leng and Y. Wu, *ACS Omega*, 2023, **8**, 7517–7528; (c) P. Meher, R. K. Samanta, S. Manna and S. Murarka, *Chem. Commun.*, 2023, **59**, 6092–6095; (d) D. Chen, X. Yang, D. Wang, Y. Li, L. Shi and D. Liang, *Org. Chem. Front.*, 2023, **10**, 2482–2490; (e) G. C. Upreti, T. Singh, K. Khanna and A. Singh, *J. Org. Chem.*, 2023, **88**, 4422–4433; (f) J.-Z. Li, L. Mei, X.-E. Cai, C.-C. Zhang, T.-T. Cao, X.-J. Huang, Y.-L. Liu and W.-T. Wei, *Adv. Synth. Catal.*, 2022, **364**, 2080–2085; (g) H.-C. Li, K. Sun, X. Li, S.-Y. Wang, X.-L. Chen, S.-Q. He, L.-B. Qu and B. Yu, *J. Org. Chem.*, 2021, **86**, 9055–9066; (h) L. Liu, D.-Y. Yang, Y.-H. He and Z. Guan, *J. Org. Chem.*, 2020, **85**, 11892–11901; (i) Y. Yuan, Y. Zheng, B. Xu, J. Liao, F. Bu, S. Wang, J.-G. Hu and A. Lei, *ACS Catal.*, 2020, **10**, 6676–6681.



- 23 (a) M. Lu, W. Xu and M. Ye, *Molecules*, 2023, **28**, 736–746; (b) Z.-J. Liu, J.-F. Li, F.-P. Zhang, X.-T. Xu and M. Ye, *Org. Lett.*, 2023, **25**, 353–357; (c) S.-J. Lou, Z. Mo, M. Nishiura and Z. Hou, *J. Am. Chem. Soc.*, 2020, **142**, 1200–1205; (d) X. Wu, G. Xiao, Y. Ding, Y. Zhan, Y. Zhao, R. Chen and T.-P. Loh, *ACS Catal.*, 2020, **10**, 14107–14116; (e) Y.-T. He, Y.-J. Mao, H.-Y. Hao, Z.-Y. Xu, S.-J. Lou and D.-Q. Xu, *Org. Lett.*, 2020, **22**, 8250–8255.
- 24 (a) H.-X. Jin, Y. Zhu, J. Zhang, Y.-P. Zhang, L. Zhu, L. Long, Z. Chen, H. Luo and D. Yu, *Org. Chem. Front.*, 2024, **11**, 5762–5768; (b) Y. Liu, Z. Li, L. Yang, S. Li and Z. Chen, *Org. Biomol. Chem.*, 2023, **21**, 8690–8694; (c) Y. Wu, H. Liu, L. Liu and J.-T. Yu, *Org. Biomol. Chem.*, 2023, **21**, 7079–7084; (d) B. Sun, H.-X. Tian, Z.-G. Ni, P.-Y. Huang, H. Ding, B.-Q. Li, C. Jin, C.-L. Wu and R.-P. Shen, *Org. Chem. Front.*, 2022, **9**, 3669–3676; (e) Z. Guo, X. Chen, Y. Xue, J. Li, D. Zou, Y. Wu and Y. Wu, *Adv. Synth. Catal.*, 2022, **364**, 4231–4236.
- 25 S.-N. Lin, Y. Chen, X.-D. Luo and Y. Li, *Eur. J. Org. Chem.*, 2021, **31**, 4485–4489.
- 26 Z. Chen, Z. Li, S. Li, G. Qian and Y. Sun, *New J. Chem.*, 2023, **47**, 11465–11470.
- 27 Q.-H. Zhou, J.-Y. Dai, W.-J. Zhao, X.-Y. Zhong, C.-Y. Liu, W.-W. Luo, Z.-W. Li, J.-S. Li and W.-D. Liu, *Org. Biomol. Chem.*, 2023, **21**, 3317–3322.
- 28 P. Huang, C. Lv, H. Song, C. Wang, J. Du, J. Li, B. Sun and C. Jin, *Green Chem.*, 2024, **26**, 7198–7205.
- 29 (a) R. Ma, Y. Ren, Z. Deng, K.-H. Wang, J. Wang, D. Huang, Y. Hu and X. Lv, *Molecules*, 2022, **27**, 8389–8397; (b) S. Lin, J. Cui, Y. Chen and Y. Li, *J. Org. Chem.*, 2021, **86**, 15768–15776.
- 30 Y. Pang, J. Yan, N. Al-Maharik, Q. Zhang, Z. Fang and D. Li, *Beilstein J. Org. Chem.*, 2025, **21**, 234–241.
- 31 S.-N. Lin, Y. Deng, H. Zhong, L.-L. Mao, C.-B. Ji, X.-H. Zhu, X. Zhang and B.-M. Yang, *ACS Omega*, 2024, **9**, 28129–28143.

